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REVIEW ARTICLE

Role of nutraceuticals in gut health and growth performance of poultry

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Abstract The gut is a fundamental organ system which makes up two equally important functions, i.e., the digestion and host defence. To elicit the well-functioning and healthy gut, the dynamic balance of gut ecosystem is of importance. A wide range of factors related to diets and infectious disease agents seem to affect this balance, and subsequently affect the health status and production performance of the chicken. With the ban and/or reduction of the use of antibiotic growth promoters (AGPs) in poultry production, the alternatives to AGP are needed especially to preserve the balance of gut microbiota in chicken. This review provides a summary of the potentials and possible mechanisms of action of some alternatives to AGP (referred as nutraceuticals) in improving the gut microbial ecosystem and immune system as well as growth performance of poultry.

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1. Introduction

The high growth rate and feed efficiency are the two main targets in poultry production. A number of factors should be taken into consideration for the optimum performance of birds including genetic potential of the birds, quality of the diets, environmental condition and disease outbreaks. Apart from these mentioned-factors, gut health has recently been the subject of intense studies in poultry production (Rinttilä and Apajalahti, 2013). The gut is a pivotal organ system which mediates nutrient uptake and use by the animals. The gut is also a major site of potential exposure to environmental pathogens (Yegani and Korver, 2008). Hence, a well-functioning and healthy gut is the cornerstone of the optimum performances of the birds. When the gut function and health are impaired, digestion and absorption of nutrients are affected and thus the health and performance of birds will be compromised.

Besides responsible for the absorption of nutrients from the lumen, intestinal mucosa of broiler chicken plays an important role in providing an effective barrier between the hostile luminal content and the host internal tissues. In this notion, intestinal mucosa is an important determinant of gut health and performance of chicken (Rinttilä and Apajalahti, 2013). To support the intestinal mucosal barrier functions, the dynamic balance between the mucus layer, epithelial cells, microbiota and immune cells in the intestine is of importance (Schenk and Mueller, 2008). A number of factors associated with diet and infectious disease agents have been reported to affect this dynamic balance, and subsequently affect the health status and production performance of the chicken (Yegani and Korver, 2008). A subtherapeutic use of antibiotics has been widely practiced in poultry industry for decades to maintain the balance of ecosystem in the gut as well as to improve the growth performance of chicken (Huyghebaert et al., 2011). However, this practice has been questioned, given the increasing prevalence of resistance to antibiotics in chicken (Kabir, 2009). Hence, alternatives to antibiotics are needed in poultry industry to maintain the gut health and promote the performance of birds.

Of the factors that may be responsible for the gut health and performance of chicken, commensal microbiota in the gut seem to have pivotal roles as they may help to direct the development of gut structure and morphology, modulate the immune responses, offer protection from luminal pathogens as well as aid digestion and utilization of the nutrients (Rinttilä and Apajalahti, 2013). In their review, Yegani and Korver (2008) suggested that gut microbial profile can be affected by diet, in which the changes in dietary composition may result in the alteration of the microbial community in the gut. In addition to that, some foods or food ingredients have been reported to modulate the gut microbiota and immune system which may be beneficial for the chicken, referred as nutraceuticals (Huyghebaert et al., 2011).

The objectives of this review are to describe the potentials and possible mechanisms of action of some nutraceutical compounds (e.g., probiotics, prebiotics, synbiotics, organic acids, exogenous enzymes, polyunsaturated fatty acids [PUFAs] and phytobiotics) in improving the gut microbial ecosystem and immune system as well as growth performance of poultry. The applications of nutraceuticals for prevention and/or treatment of enteric infections in poultry are also briefly summarized in this review.

2. Gut microbiota, defence system and performance of birds

Similar to mammals, the immune system of birds is complex and composed of several cells and soluble factors that work together to produce a protective immune response (Yegani and Korver, 2008). It has been known that commensal gut microbiota is important inducers for the development and maturation of both innate defence mechanisms and adaptive immune responses of chicken (Muir et al., 2000; Haghighi et al., 2006; Brisbin et al., 2008). Based on the studies in mammals, specific commensal bacterial species may also have a vital role in inducing the accumulation of certain immune cell populations in the intestine (Kogut, 2013). For example, bacteria belonging to the phylum *Bacteroidetes* (i.e., *Bacteroides fragilis*) have been shown to be associated with the development of interleukin-17 (IL-17) producing T-helper cells (Mazmanian et al., 2005). Lactobacilli are a group of commensal bacteria that have long been known for their ability to activate the intestinal immune system and increase the resistance to diseases, in part through the release of low-molecular-weight peptides which induce immune activation (Muir et al., 2000). These bacteria have also been reported to produce a wide variety of short chain fatty acids (SCFAs), which are bacteriostatic for a subset of bacterial species either directly or by reducing pH of the intestinal environment, produce bacteriocins with microbicidal or microbiostatic properties and contribute to the colonization resistance against pathogenic microbes by modifying the receptors used by the pathogenic bacteria (Adil and Magray, 2012; Rinttilä and Apajalahti, 2013). Moreover, SCFAs produced by lactic acid bacteria (LAB) favour the renewal and barrier function of the gastrointestinal epithelium (Kogut, 2013).

The intestine contains both bacteria that are beneficial for the health, such as gram-positive lactobacilli and bifidobacteria, and potential pathogenic bacteria, such as *Clostridium* spp., *Salmonella* and *Escherichia coli*. It is generally accepted that a proper bacterial balance between the number of beneficial bacteria and bad bacteria in the intestine (at least 85% of total bacteria should be good bacteria) is vital for the host, and the impact on gut health often comes from microbial imbalance in the gut of chicken (Choct, 2009). This microbial imbalance will be exacerbated when antibiotics are withdrawn from feed (Choct, 2009). By dietary means, it is possible to modify the gut microbial population, concomitant with the growth of favourable bacteria in the gut of chicken (Adil and Magray, 2012).

Apart from the defence systems, the importance of intestinal microbiota for the performance of broiler chicken has been the focus of studies for decades. In the review of Kogut (2013) and Rinttilä and Apajalahti (2013), it is suggested that commensal intestinal bacteria are important in digestion and synthesis of dietary compounds and involved in the development of gastrointestinal tract. These bacteria also play important roles in the regulation of intestinal epithelial proliferation, host energy metabolism and vitamin synthesis. Based on the study in mammals, commensal bacteria contribute to the regulation of digestion by mediating the bile acid synthesis, lipid absorption, amino acid metabolism, vitamin synthesis and SCFA production (Brestoff and Artis, 2013). Moreover, commensal bacteria influence the activity of digestive enzymes and gut mucosal morphology of the chicken (Lan et al., 2005). It should be noted that although the gut microbiota have potential benefits on the digestion (of certain dietary components especially non-digestible carbohydrate), it may have an adverse effect on the utilization of energy by the host, especially when dietary energy is supplied in the form of substrates which are easily digestible by the chicken itself (Lan et al., 2005). In the latter condition, no/less substrate (non-digestible carbohydrate) is available for the gut microbiota, resulting in a competition for the substrate between the host and gut microbiota. In this circumstance, it is generally agreed that gut microbiota is a nutritional "burden" in fast-growing broiler chickens (Yang et al., 2009), where easily digestible feed is usually provided to the broiler chicken.

The balance of intestinal microbiota is important to promote the healthy gut and maximum growth performance of chickens (Kabir, 2009). The shift of microbiota can affect the morphology of the intestinal wall and induce immune reactions, which can have in turn impact on the energy expenses and growth of the chickens (Humphrey and Klasing, 2003). Likewise, the intestinal colonization by pathogens may induce the immune response that eventually diverts energy and nutrients away from growth to the acute requirement of combating infections (DiAngelo et al., 2009). In chicken, the inflammatory response is important for dealing with microbial infections (Kogut, 2013). However, if left uncontrolled, this immune activation would pose a risk of excessive inflammation and intestinal damage, which may in turn impair the digestive functions of the intestine (Brisbin et al., 2008). Moreover, the excessive inflammation may also cause disturbances in host metabolism (Kogut, 2013). It has been reported that commensal microbiota in the gut play important roles in the maintenance of intestinal immune homeostasis and prevention of intestinal inflammation (Lan et al., 2005). Through their products (SCFAs), the commensal bacteria may exert anti-inflammatory activities, thus preventing the intestinal damage (Brestoff and Artis, 2013). Taken together, the balance of intestinal microbiota is crucial for the intestinal homeostasis and healthy/normal functions (digestive and defence) of the gut of chicken.

3. The use of antibiotics in poultry production

The use of antibiotics as growth promoters in poultry feed has been practiced worldwide during the last 50 years (Yegani and Korver, 2008). This application has been acknowledged to improve feed conversion and growth, and reduce morbidity and mortality due to clinical and subclinical diseases. The mechanisms through which antibiotics promote the growth of chickens are still not exactly known, but study with germ-free chicken indicates that the growth promoters are mediated by their antimicrobial effect (Yang et al., 2009). Antibiotics may reduce the microbial load in the gut leading to more nutrient availability for the host (Brisbin et al., 2008). Beyond the beneficial features, the risk concerning the development of antimicrobial resistance and transference of antibiotic resistance genes from animal to human microbiota led the European Union to ban the application of antibiotics as growth promoters since 1st January 2006, which was followed by the other parts of the world including North America (Yegani and Korver, 2008). The removal of AGP from poultry diets has led to animal performance problems and a rise in the incidence of certain poultry diseases, such as (subclinical) necrotic enteritis and dysbacteriosis (Huyghebaert et al., 2011). To date, the need to find alternatives for AGP is therefore important.

4. Nutraceutical application in poultry

Ideally, the alternatives to AGP should have the same beneficial effect as AGP. In recent years, nutrition-based research to find the alternatives to AGP has been greatly intensified in farm animals including poultry (Huyghebaert et al., 2011). There are a number of foods or food components that provide beneficial roles (for growth and health) beyond ordinary nutrition, leading to the development of the concept of nutraceuticals. In general, nutraceuticals can be defined as food or food components that have a role in modifying and maintaining normal physiological functions that support the healthy host (Das et al., 2012). These nutraceuticals also help in protecting the host against infectious diseases (Cencic and Chingwaru, 2010). Nutraceuticals may range from isolated nutrients (vitamin, mineral, amino acids, fatty acids, etc.), herbal products (polyphenols, herbs, spices, etc.), dietary supplements (probiotics, prebiotics, synbiotics, organic acids, antioxidants, enzyme, etc.) to genetically modified foods (Das et al., 2012).

In humans, nutraceutical products have been used as alternative therapies for cancer, diabetes, osteoporosis, depression, etc. (Das et al., 2012). Owing to the potential benefits of nutraceuticals in modulating the gut microbial populations and immune systems of the host (Cencic and Chingwaru, 2010), the use of nutraceuticals for prevention and/or treatment of enteric infections in the chicken may be considered. The involvement of nutraceuticals in improving of intestinal morphology and nutrient absorption (Awad et al., 2008; Hassanpour et al., 2013) may also encourage the nutritionists to include these compounds in the diet to promote the growth performance of birds.

4.1. Probiotics

Probiotics are single or mixed culture of living microorganisms which when administrated in adequate numbers exert health benefits for the host by improving the host intestinal microbial balance, enhancing of colonization resistance against pathogens and improving the immune responses (Kabir, 2009; Brisbin et al., 2010; Cencic and Chingwaru, 2010; Das et al., 2012). The species of microorganisms currently being used in probiotic preparations are varied, and LAB, i.e., *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus helveticus*, *Lactobacillus lactis*, *Lactobacillus salivarius*, *Lactobacillus plantarum*, *Streptococcus thermophilus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Bifidobacterium* spp., are the most common type of bacteria used as probiotics (Khaksefidi and Rahimi, 2005; Kabir, 2009). Table 1 shows the examples of probiotic strains and their effects on the gut microbial population and immune responses of the birds.

The definite mechanism through which probiotics may improve the defence and performance of chickens remains unclear, but some possible mode of actions have been proposed: (1) maintaining a healthy balance of bacteria in the gut by competitive exclusion (the process by which beneficial bacteria exclude potential pathogenic bacteria through competition for attachment site in the intestine and nutrients) and antagonism (inhibit the growth of pathogenic bacteria by producing for example lactic acids), (2) promoting the gut maturation and integrity, (3) modulating the immune system and preventing inflammation (4) improving the metabolism by increasing digestive enzyme activity and decreasing bacterial enzyme activity and ammonia production, (5) improving feed intake and digestion (as a result from the improved microbial balance in the gut), and (6) neutralizing enterotoxins and stimulating the immune system (Jin et al., 1997; Khaksefidi and Rahimi, 2005; Lan et al., 2005; Haghighi et al., 2006; Kabir, 2009; Brisbin et al., 2010).

The effect of probiotic administration on the performance of chicken is variable. Khaksefidi and Rahimi (2005) reported

Table 1 Examples of probiotic effects on the gut microbiota and immune system of birds.

Strains of probiotic	Biological activities	References
Effects on gut microbiota:		
Probiotic containing *L. acidophilus*, *L. casei*, *B. bifidum*, *A. oryzae*, *S. faecium* and *Torulopsis* spp.	Lowered numbers of *coliform* and *Campylobacter* in the gut	Khaksefidi and Rahimi (2005)
L. agilis JCM 1048 and *L. salivarius* subsp. *Salicinius* JCM 1230	Enriched the diversity of *Lactobacillus* flora in jejunum and caecum by increasing the abundance and prevalence of *Lactobacillus* spp. inhabiting the intestine. Restored the microbial balance and maintained the natural stability of indigenous bacterial microbiota in the gut	Lan et al. (2004)
L. salivarius	Reduced the number of *S. enteritidis* and *C. perfringens* in the gut	Kizerwetter-Swida and Binek (2009)
Probiotic containing *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and *Pediococcus* strains	Increased the concentrations of bacteria belonging to *Bifidobacterium* spp., *Lactobacillus* spp. and gram-positive cocci	Mountzouris et al. (2007)
L. acidophilus	Competed with pathogenic *E. coli* in the gut of gnotobiotic chicks	Watkins et al. (1982)
L. salivarius CTC2197	Reduced *S. enteritidis* C-114 colonization of the gut *in vivo*	Pascual et al. (1999)
L. reuteri C1, C10 and C16; *L. gallinarum* I16 and I26; *L. brevis* I12, I23, I25, I218 and I211, and *L. salivarius* I24	Increased the caecal populations of lactobacilli and bifidobacteria and decreased the caecal *E. coli*	Mookiah et al. (2014)
Effects on immune system:		
Commercial probiotic containing *L. acidophilus*, *B. bifidum* and *S. faecalis*	Increased production of antibodies at the systemic and local (intestinal) level	Haghighi et al. (2006)
L. acidophilus	Induced T-helper-1 cytokines in caecal tonsil cells	Brisbin et al. (2010)
L. salivarius	Induced anti-inflammatory responses (interleukin [IL]-10 and transforming growth factor [TGF]-β) in caecal tonsil cells	Brisbin et al. (2010)
Commercial probiotics containing *L. plantarum*, *L. bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *B. thermophilus*, *E. faecium*, *A. oryzae* and *C. pintolopessi*	Increased the production of antibodies. Increased the weight of spleen and bursa of the chicken	Kabir et al. (2004)
Lactobacillus-based probiotic	Altered intestinal intraepithelial lymphocyte (IEL) subpopulations. Stimulated secretions of interferon [IFN]-γ and IL-2 against *E. acervulina*	Dalloul et al. (2003)
Commercial probiotics containing *L. plantarum*, *L. bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *B. bifidum*, *S. thermophilus*, *E. faecium*, *A. oryzae* and *C. pintolopessi*	Increased antibody titre against Newcastle disease (ND). Increased the geometric means haemagglutination inhibition (HI) titres of birds	Khan et al. (2011)
B. subtilis Bs964, *C. utilis* BKM-Y74 and L. acidophilus LH1F	Enhanced intestinal mucosal immunity of the chicken at the early age	Yurong et al. (2005)

that inclusion of probiotics in the diet resulted in improved performance of broiler compared to the control group in the 4th, 5th and 6th weeks, whilst Bai et al. (2013) reported no significant differences in growth performance during 22–42 days between broilers fed the probiotic diet and those fed control diet. The differences in the dose and nature of probiotics administrated and variation in the physiological state of the birds are likely the reasons (Huyghebaert et al., 2011). In terms of immune responses, different species and/or strains of probiotics may have different immunomodulatory activities due to the ability of probiotics to induce cytokine production, which leads to modulation of innate and adaptive immune responses (Brisbin et al., 2010). In caecal tonsil cells of chicken, Brisbin et al. (2010) noticed that *L. acidophilus* was more effective in inducing T-helper-1 cytokines whilst *L. salivarius* induces a more anti-inflammatory response. In accordance with the immune responses, the competitive exclusion and antagonistic activity of probiotics seem to be species and strain specific as well (Hütt et al., 2006).

4.2. Prebiotics

Prebiotics are non-digestible feed ingredients that beneficially affect the host by selectively altering the composition and metabolism of the gut microbiota (Huyghebaert et al., 2011; Das et al., 2012). Prebiotics may provide energy for the growth of endogenous favourable bacteria in the gut, such as bifidobacteria and lactobacilli, thus improving the host microbial balance (Das et al., 2012). In this notion, prebiotics may have more benefits compared with probiotics, in that prebiotics stimulate the bacteria (commensal bacteria) which have adapted to the environment of gastrointestinal tract (Adil and Magray, 2012; Alloui et al., 2013). Prebiotics have been reported to enhance host defence and reduce mortality of bird caused by the invasion of gut pathogens (Ganguly, 2013). The mechanism by which prebiotics exert this feature remains less elucidated, but it is likely that the capacity of prebiotics to increase the number of LAB in the gut may aid the competitive exclusion of pathogens from the gastrointestinal tract of birds (Alloui et al., 2013). The increased production of SCFAs with administration of prebiotics resulting in increased intestinal acidity may also contribute to the suppression of pathogens in the gut of chicken. Prebiotics have also been reported to enhance the immune response of chicken, resulting in rapid clearance of pathogens from the gut (Kim et al., 2011). With regard to the immune-enhancing effect of prebiotics, this may in part be due to direct interaction between prebiotics and gut immune cells as well as due to an indirect action of prebiotics via preferential colonization of beneficial microbes and microbial products that interact with immune cells (Janardhana et al., 2009). Overall, prebiotics may have a similar mechanism as probiotic in supporting the gut health of chicken (Huyghebaert et al., 2011). The most common prebiotics used in poultry are oligosaccharides, including inulin, fructooligosaccharides (FOS), mannanoligosaccharides (MOS), galactooligosaccharides (GOS), soya-oligosaccharides (SOS), xylo-oligosaccharides (XOS), pyrodextrins, isomalto-oligosaccharides (IMO) and lactulose (Huyghebaert et al., 2011; Kim et al., 2011; Alloui et al., 2013). Table 2 shows some examples of prebiotics and their effects on the gut microbiota and immune system of birds.

Table 2 Examples of prebiotic effects on the gut microbiota and immune system of chicken.

Type of prebiotics	Biological activities	References
Effects on gut microbiota:		
FOS	Reduced intestinal colonization by *Salmonella*	Bailey et al. (1991)
FOS or MOS	Decreased populations of C. perfringens and E. coli in the gut	Kim et al. (2011)
FOS	Provided nutrients for the growth of beneficial bacteria in the gut	Alloui et al. (2013)
FOS	Increased the population of *Bifidobacterium* in the small intestine and colon. Increased the population and diversity of lactobacilli in the ileum	Bouhnik et al. (1996), Campbell et al. (1997), Kim et al. (2011)
Inulin	Increased bifidobacterium counts and decreased *E. coli* counts in caecal contents	Nabizadeh (2012)
GOS	Increased *Bifidobacterium* spp. and decreased *Campylobacter* spp. in the faecal samples	Baffoni et al. (2012)
IMO	Increased the caecal populations of lactobacilli and bifidobacteria and decreased the caecal *E. coli*	Mookiah et al. (2014)
Effects on immune system:		
FOS or MOS	Affected the heterophil:lymphocyte ratio and basophil levels	Kim et al. (2011)
FOS and MOS	Increased serum concentration of IgA	Kim et al. (2009)
MOS	Increased serum concentration of IgG and IgM	Cetin et al. (2005)
Commercial prebiotic (Fibregum and Raftifeed-IPE)	Increased serum concentration of IgA and IgM, and enhanced systemic immune capacity in chickens	Vidanarachchi et al. (2013)
FOS	Enhanced the IgM and IgG antibody titres in plasma	Janardhana et al. (2009)
Prebiotic-based MOS and β-glucan	Increased the relative weight of spleen, decreased the heterophil-to-lymphocyte ratio and increased antibody titres against *S. enteritidis*	Sadeghi et al. (2013)

It has been reported that increased production of SCFAs in the gastrointestinal tract due to prebiotics may benefit the host by recovering some of the lost energy from competition with bacteria (Ganguly, 2013). Owing to this, dietary prebiotic supplementation is attributable to the improved bird performance and energy utilization (Yang et al., 2008a; Choct, 2009; Nabizadeh, 2012). In agreement with the previous works, Kim et al. (2011) reported that supplementation of prebiotics to the diet improved the weight gain of broiler when compared with the control, although differences in feed intake, feed conversion and mortality were not observed. Different from the previous authors, Biggs et al. (2007) and Janardhana et al. (2009) did not show a significant weight gain in prebiotic groups compared to controls. These discrepancies may be explained by different types of prebiotics used in the study, as different types of prebiotics may have different growth promoting effects (Kim et al., 2011). In accordance with this, Huyghebaert et al. (2011) in their review suggested that the nature/characteristic and type of prebiotics may determine the mechanism of action of prebiotics as alternative to AGP. For instance, inulin and FOS are preferable substrates for bifidobacteria and therefore promote the growth of bifidobacteria in the gut, whereas MOS have receptor properties for fimbriae of *E. coli* and *Salmonella* spp. Owing to these conditions, inulin and FOS tend to provoke the binding of bifidobacteria to host intestinal mucosa and thus hinder the binding of pathogenic bacteria to the host intestine, whereas MOS (act as receptor analogue for the pathogens) may bind the pathogens and lead to elimination of pathogens with the digesta flow (Huyghebaert et al., 2011).

4.3. Synbiotics

Both probiotics and prebiotics have been shown to provide the beneficial effects on the gut of birds. When probiotics and prebiotics are combined, they form synbiotics (Huyghebaert et al., 2011). This combination could improve the survival and persistence of the health-promoting organism in the gut of birds because its specific substrate is available for fermentation (Yang et al., 2009; Adil and Magray, 2012). Several studies have shown the potential benefits of synbiotics on the intestinal microbial ecosystem and immune functions of chicken (Table 3). In terms of performance, synbiotics were effective in improving the growth of broiler, which corresponded to the effect of inclusion of either probiotics or prebiotics in the diet of chickens (Abdel-Raheem et al., 2012; Mookiah et al., 2014). The improvement of intestinal morphology and nutrient absorption due to feeding synbiotics seems to contribute to the enhanced performance of broiler chicken (Awad et al., 2008; Hassanpour et al., 2013).

It has been suggested that synbiotics are much more efficient when used in combinations than singly (Alloui et al., 2013), in that Fukata et al. (1999) reported in broilers that a probiotic and FOS each reduced intestinal *S. enteritidis* colonization when used singly, but their combination was more effective. This was, however, in contrast with the more recent study by Mookiah et al. (2014) who reported that synbiotics did not show a two-fold synergistic effects, when compared to those of multi-strain probiotic (consisting of 11 *Lactobacillus* strains) or prebiotic (IMO) alone, in terms of the performance, caecal bacterial populations and concentrations of caecal volatile fatty acids (VFA) and non-VFA of broiler chickens. The discrepancy may be explained by the differences in the strain of probiotics and/or type of prebiotics used.

4.4. Organic acids

Organic acids, such as lactic, acetic, tannic, fumaric, propionic, caprylic acids, etc., have been shown to exhibit beneficial

Table 3 Examples of synbiotic effects on the gut microbiota and immune system of birds.

Type of synbiotics	Biological activities	References
Effects on gut microbiota:		
Commercial synbiotics (Biomin Imbo)	Increased the LAB population and reduced *E. coli* and total *coliform* populations in the intestine	Dibaji et al. (2014)
Bifidobacterium-based synbiotic product	Reduced C. jejuni concentration in poultry faeces	Baffoni et al. (2012)
Synbiotic (*S. cerevisiae* plus MOS)	Reduced the number of *E. coli* in the small intestinal and caecal digesta	Abdel-Raheem et al. (2012)
Synbiotic (11 *Lactobacillus* strains plus IMO)	Increased the caecal populations of lactobacilli and bifidobacteria and decreased the caecal *E. coli*	Mookiah et al. (2014)
Synbiotic (*E. faecum* plus FOS)	Reduced the intestinal colonization by *C. perfringens*	El-Ghany (2010)
Synbiotic (probiotic plus FOS)	Reduced intestinal *S. enteritidis* colonization	Fukata et al. (1999)
Effects on immune system:		
Commercial synbiotic (Biomin Imbo)	Increased antibody production	Hassanpour et al. (2013)
Synbiotic (*L. lactic* plus raffinose family oligosaccharides)	Stimulated the expression of IL-6 and IFN-γ during *in vitro* culturing of chicken lymphocytes	Slawinska et al. (2012)
Synbiotic (combination of *Lactobacillus*, *Bifidobacterium* and oligosaccharides derived from yeast cell wall)	Improved the antibody response to NDV and infectious bronchitis virus (IBV) vaccines	El-Sissi and Mohamed (2011)

effects on the intestinal health and performance of birds (Adil et al., 2010; Saki et al., 2012; Menconi et al., 2014). Saki et al. (2012) reported that supplementation of organic acids in the diet increased LAB counts in the ileum and caecum of broiler chicken. This treatment also significantly decreased *Enterobacteriaceae* and *Salmonella* counts in the intestine of birds (Cengiz et al., 2012; Saki et al., 2012). In terms of performance, feeding organic acids resulted in improved body weight gains and feed conversion ratio (Adil et al., 2010). Antimicrobial property of acids has been suggested to play a crucial role in controlling the population of pathogenic bacteria in the gut of birds (Partanen and Mroz, 1999). The ability of acids to change from undissociated to the dissociated form, the pKa value and hydrophobicity of acids may determine the effectiveness of the compounds as antimicrobial agents in the gut of birds. In the undissociated form, organic acids can freely diffuse through the semi-permeable membrane of the bacteria into the cell cytoplasm (Van Immerseel et al., 2006). Once in the cell, where the pH is maintained near 7, the acid will dissociate and suppress bacterial cell enzymes (e.g., decarboxylases and catalases) and nutrient transport systems (Huyghebaert et al., 2011). The dissociation constant (pKa), that is the pH at which the acid is half dissociated, is one of the most important characteristic of organic acids. In general, organic acids with higher pKa values are more effective antimicrobial compounds (Huyghebaert et al., 2011). Given that the bacterial cell wall normally contains lipid material, hydrophobicity is thereof an important feature of organic acids to exert its antimicrobial activity, in that hydrophobic organic acids can interact with this lipid material in a way that disrupts microbial activity (Kuroda et al., 2009; Huyghebaert et al., 2011).

The reduction of pathogenic intestinal bacteria, which produce toxin causing damage of intestinal villi and crypt structure, is associated with the improved gut structure of chickens (Dibner and Buttin, 2002). In concert with the antimicrobial effect, inclusion of organic acids seems to have direct effects on the histomorphology of the gut by increasing the height of villus (Adil et al., 2010, 2011). Herein, supplementation of organic acids may facilitate the nutrient absorption and that in turn growth performance in broiler chicken (Adil et al., 2010). The potential of organic acids in lowering chyme pH is another property of this compound to support the growth, as this feature may increase protein digestion (Gauthier, 2002). Although supplementation of organic acids has been evidenced to support the health and performance of birds, the use of organic acids must be administrated in low dosage, as excessive dosage may result in growth depression in intestinal villus height and width, as well as crypt depth (Smulikowska et al., 2010).

Organic acids are widely distributed in nature as normal constituents of plants or animal tissues. They are also products of microbial fermentation of carbohydrates especially in the caeca of birds (Huyghebaert et al., 2011). A wide range of organic acids with variable physical and chemical properties are available for poultry, of which many are used in the drinking water or mixed with the feed (Huyghebaert et al., 2011; Menconi et al., 2014). In the market, organic acids can be found in the form of single or in combination (Menconi et al., 2014). It has been suggested that combinations of organic acids are more effective than supplements that contain only one type of acid. This is because different types of organic acids diffuse through the bacterial cell wall and membrane and into the cell cytoplasm at different rates. These acids dissociate to form a conjugate base and a free hydrogen ion at different rates and respective pKa values (Novus International Inc., 2006).

4.5. Exogenous enzymes

Various exogenous enzymes including β-glucanase, xylanase, amylase, α-galactosidase, protease, lipase, phytase, etc. have been supplemented in poultry diets for decades (Adeola and Cowieson, 2011; Bedford and Cowieson, 2012). The use of exogenous enzymes is of importance in poultry given that chicken diets are composed primarily of corn and soybean meal, which contain varying levels of different anti-nutritive factors (e.g., non-starch polysaccharides [NSP] and protease inhibitors) that can impede normal digestion and absorption processes of nutrients in the digestive tract (Yegani and Korver, 2013). The tendency to use non-conventional ingredients (containing anti-nutritional factors and fibre) in poultry diet to reduce the cost of feeding may also encourage the use of exogenous enzyme, as these materials cannot be fully digested and utilized by the chickens (Costa et al., 2008). In this context, the exogenous enzymes are used to correct the lack of specific endogenous enzymes for digesting certain nutrients in various feedstuffs or to hydrolyse anti-nutritional factors in feed ingredients (Ao, 2005). Enzyme supplementation is also important for environmental issues, as it may reduce the pollutant potential of excreta (Costa et al., 2008).

Exogenous enzymes have been reported to modulate the gut microbiota of birds, which may in turn affect the health status of the host and the extent of digestion accomplished by the host (Bedford and Cowieson, 2012). Adeola and Cowieson (2011) revealed that carbohydrase supplementation increased the proportion of lactic and organic acids, reduced ammonia production, and increased VFA concentration which is indicative of hydrolysis fragmentation of NSP and supporting growth of beneficial bacteria. The study by Vahjen et al. (1998) showed that the counts of lactobacilli associated with gut tissue were increased in birds given a xylanase supplemented diet during the first week and remained stable thereafter. Concomitant with this, adding xylanase in the diet reduced the number of *coliform* and *Salmonella*, and increased the number of *Lactobacillus* in the ileum of chicken (Nian et al., 2011). Exogenous enzymes are also beneficial to prevent the horizontal transmission of *Salmonella* infection between the birds (Amerah et al., 2012). Unlike the previous studies, Yang et al. (2008b) reported that xylanase supplementation did not alter the number of mucosa-associated lactobacilli and *coliform* in the jejunum of birds. A number of factors such as diet composition, animal strain, sex and age, and digesta flow rate along with the type of enzyme employed may explain these discrepancies (Yang et al., 2008b; Adeola and Cowieson, 2011). Apart from that, the change in the gut microbial populations due to exogenous enzymes may influence the immunity of the chicken, in part through the role of LAB in the intestine of the birds (Bedford and Cowieson, 2012).

Besides modulating the gut microbiota and increasing the digestibility of the feed, the growth-promoting effects of enzymes also appear to be partly related to the mucosal morphology of the small intestine of birds. Yang et al. (2008b) reported that the crypt depth of jejunum was reduced by xylanase and this was associated with the increased growth of chicken fed xylanase. Concomitantly, Adeola and Cowieson (2011) revealed that carbohydrase supplementation improved villi length and supported the growth of chicken. Furthermore, reduction in the viscosity of intestinal contents is associated with the growth-promoting effects of enzymes, as with reduced viscosity, enzymatic action on intestinal content is more efficient (Costa et al., 2008; Adeola and Cowieson, 2011).

To exert their functions, the activity of enzymes must not be affected by processing or by the low pH (<4) or endogenous digestive enzymes in the digestive tract of chickens (Ao, 2005). To obtain the maximum benefit from the enzymes, the use of multiple enzymes is recommended as the combination of the enzymes may target different anti-nutritive compounds in the feedstuffs (Adeola and Cowieson, 2011). However, it should be noted that the beneficial effect of enzyme combination may be dependent on the diet composition (Meng et al., 2005). Hence, understanding how the enzyme works together to hydrolyse their respective substrates is critical to maximize the efficacy of enzyme combinations.

4.6. Polyunsaturated fatty acids

Polyunsaturated fatty acids which include *n*-3 and *n*-6 fatty acids are essential to the body's function such as immunity (Cencic and Chingwaru, 2010). In poultry, fish oil and corn oil are the main source of *n*-3 fatty acids and *n*-6 fatty acids, respectively. Yang and Guo (2006) reported that fish oil supplementation enhanced the immune response (increased sIgA secretion in the jejunum), whereas corn oil reduced it. Moreover, Maroufyan et al. (2012) reported that dietary n-3 PUFAs (combination of tuna oil, sunflower oil and palm oil) improved the immune responses of birds, as evidenced by the increase in spleen weight, and infectious bronchitis disease (IBD) and ND antibody titres and IL-2 and IFN-γ concentrations. Different from the earlier works, Al-Khalifa et al. (2012) reported that dietary n-3 PUFA (fish oil) decreased the immune response (phagocytosis and lymphocyte proliferation) in broiler chickens. Conjugated linoleic acid (CLA) is another type of PUFA that has been used to supplement the poultry diets. Zhang et al. (2005) reported that CLA enhanced the immune response of chicken. Similarly, He et al. (2007) reported that moderate dietary CLA promoted the growth of immune tissues, such as the thymus and bursa, stimulated T lymphocyte proliferation and elevated antibody production in chickens. Altogether, the biological variations of birds (e.g., strain, sex, age, etc.), type of the essential fatty acids, dietary composition and the ratio between n-3 to n-6 fatty acids in the diet seem to affect the immune response of birds fed PUFAs.

In vitro study showed that *n*-3 PUFAs possess antimicrobial activities (Kankaanpää et al., 2001). Concomitant with this, study in rats demonstrated that fish oil supplementation decreased *Bacteroidaceae* and increases *Bifidobacteriaceae* numbers in the gut compared with a standard chow diet (Hekmatdoost et al., 2008). Different from the mammal study, Geier et al. (2009) reported that n-3 PUFAs supplementation did not alter the overall microbial communities in the intestine of chicken, and only little influence on the overall intestinal microbiota and *Lactobacillus* profile was observed. With regard to CLA, supplementation of this fatty acid was able to maintain the number of LAB in the gut of chicken throughout the rearing period, whilst the LAB was reduced in the chicken fed control diet during the first three weeks of rearing (Chanuwat et al., 2011).

The performance-enhancing effects of PUFAs on poultry so far remain disputable. Whereas Roy et al. (2008) and Chanuwat et al. (2011) reported that dietary supplementation of *n*-3 PUFAs (eciosapentaenoic and docosahexaenoic) or CLA promotes the growth of birds, Zhang et al. (2005) and Cho et al. (2013) did not find any effect of feeding *n*-3 PUFA (fish oil) or CLA on the growth performance of the birds. Again, the different types and sources of PUFAs, dietary composition and biological variations of the animal may explain the disputable results.

4.7. Phytobiotics

Phytobiotics are plant-derived natural bioactive compounds that can be added to the feed to improve the performance and well-being of animals (Vidanarachchi et al., 2005; Windisch et al., 2008). Phytobiotics represent a wide range of bioactive compounds that can be extracted from various plant sources, such as herbs and spices. The active compounds of phytobiotics are mostly secondary plant constituents, such as terpenoids (mono- and sesquiterpenes, steroids, etc.), phenolics (tannins), glycosides and alkaloids (present as alcohols, aldehydes, ketones, esters, ethers, lactones, etc.) (Huyghebaert et al., 2011). Based on the biological origin, formulation, chemical description and purity, Yang et al. (2009) classified phytobiotics to: (1) herbs (product from flowering, non-woody and non-persistent plants), (2) botanicals (entire or processed parts of a plant, e.g., root, leaves, bark), (3) essential oils (hydro distilled extracts of volatile plant compounds), and (4) oleoresins (extracts based on non-aqueous solvents). Antimicrobial activity and immune enhancement probably are the two major properties belonging to phytobiotics which are essential for the health and well-being of the chicken (Yang et al., 2009; Fallah et al., 2013). Table 4 shows some examples of phytobiotics with their effects on the gut microbial population and immune system in chicken.

The mechanisms by which the phytobiotics exert their benefits on the gut remain unclear, but possible mechanisms could be proposed as follows: (1) modulating the cellular membrane of microbes leading to membrane disruption of the pathogens, (2) increasing the hydrophobicity of the microbial species which may influence the surface characteristics of microbial cells and thereby affect the virulence properties of the microbes, (3) stimulating the growth of favourable bacteria such as lactobacilli and bifidobacteria in the gut, (4) acting as an immunostimulatory substance and (5) protecting the intestinal tissue from microbial attack (Vidanarachchi et al., 2005; Windisch and Kroismayr, 2007).

Studies have shown that phytobiotics improved the growth performance of broiler chickens, similar to those of AGP (Windisch and Kroismayr, 2007; El-Ghany and Ismail, 2013). Contrary results were reported by Ocak et al. (2008), Karimi et al. (2010) and Al-Mufarrej (2014) who did not observe any effect of inclusion of oregano or black cumin (*Nigella sativa* L.) powder in the chicken diet on the performance of broilers. Differences in the dietary ingredients, type and dosage of phytobiotics used in the study may explain the discrepancies. As mentioned earlier, antimicrobial activity and immune

Table 4 Examples of phytobiotic effects on the gut microbiota and immune system of birds.

Type of phytobiotics	Biological activities	References
Effects on gut microbiota:		
Acacia extract and renga renga lily extract	Increased the number of lactobacilli in the ileum of broiler chicken Caused reduction in *coliform* counts in the ileal and caecal digesta of chicken	Vidanarachchi et al. (2013)
Shiitake mushroom (*Lentinus edodes*) extract	Promoted bifidobacteria growth in the gut of broiler chickens	Willis et al. (2007)
Oregano (*Origanum vulgare*)	Exerted antimicrobial and bactericidal actions *in vitro*	Windisch and Kroismayr (2007)
Essential oils	Exerted potential antimicrobial activities against *E. coli* and *C. perfringens*	Windisch et al. (2008)
Mushroom and herb polysaccharide extracts (*Lentinus edodes* extract, *Tremella fuciformis* extract and *Astragalus membranaceus* Radix extract)	Stimulated the number of bifidobacteria and lactobacilli and reduced the number of the potentially harmful bacteria (*Bacteroides* spp. and *E. coli*)	Guo et al. (2004a)
Garlic (*Allium sativum*)	Favoured the growth of LAB and reduced the growth of *Clostridium* spp.	Filocamo et al. (2012)
Artemisia annua leaves and Artemisinin	Decreased the number of oocysts in the faeces of chickens challenged with *Eimeria*	Allen et al. (1997), Arab et al. (2006)
Essential oils extracted from herbs	Decreased *E. coli* population in ileo-caecal digesta	Jang et al. (2007)
Effects on immune system:		
Neem (*Azadirachta indica*)	Had favourable influences on immune responses of broiler chicken	Landy et al. (2011)
Chinese herbal polysaccharides (astragalan and achyranthan)	Increased microhemagglutination inhibition (HI) antibody titres and bursa of Fabricius index Increased IL-2 production of splenocytes and enhanced splenocyte proliferation in chicken	Chen et al. (2003)
Polysaccharide extracts from mushrooms (*Lentinus edodes* and *Tremella fuciformis*) and herb (*Astragalus membranaceus*)	Enhanced both cellular and humoral immune responses in *E. tenella*-infected chickens	Guo et al. (2004b)
Essential oil of *Oreganum aetheroleum*	Enhanced cell mediated and humoral immune responses of chicken against *E. coli* infections	El-Ghany and Ismail (2013)
Chinese herbal ingredients (*Astragalus* polysaccharide, isatis root polysaccharide, propolis polysaccharide and epimedium flavones)	Enhanced *in vitro* proliferation of chick embryo fibroblasts in response to the NDV infection Promoted the humoral immunity in response to NDV infection *in vivo*	Kong et al. (2006)
Epimedium polysaccharide and propolis flavones	Increased the antibody titres against ND and lymphocyte proliferation	Fan et al. (2010)
Commercial garlic extract 'Allicin oil'	Increased the HI titre to ND vaccine	Hassan et al. (2013)
Turmeric (*Curcuma longa*) extract	Enhanced levels of serum antibodies to an *Eimeria* microneme protein, MIC2, and enhanced cellular immunity as measured by concanavalin A-induced spleen cell proliferation	Kim et al. (2013)
Black cumin (*Nigella sativa* L.) powder	Enhanced immune responsiveness in broiler chickens against NDV vaccine	Al-Mufarrej (2014)

enhancement have been considered as the two major mechanisms through which phytobiotics exert beneficial effects on the health and growth performance of the chickens (Fallah et al., 2013). The phytobiotics especially those from the group of essential oils have been reported to improve flavour and palatability of feed and may thus improve the feed intake and performance of chickens (Windisch et al., 2008; Grashorn, 2010). The potential of phytogenic bioactive compounds to stimulate the proliferation and growth of absorptive cells in the gastrointestinal tract (resulting in greater villus height and deeper crypt, Jamroz et al., 2006), and to influence the production and/or activity of the digestive enzymes, e.g., increasing the activities of amylase and protease (Vidanarachchi et al., 2005; Jang et al., 2007), have also been thought to improve the growth performance of birds. Overall, it should be noted that the efficacy of phytobiotics as feed additives and their impact on the gut health and growth performance may vary as a result of the variation in their composition due to biological factors (plant species, growing location, and harvest conditions), and manufacturing (extraction/distillation, stabilization) and storage conditions (light, temperature, oxygen tension and time) (Huyghebaert et al., 2011).

Table 5 Examples of nutraceuticals for prevention and/or treatment of enteric infections in poultry.

Nutraceuticals	Enteric infections	References
Probiotic culture (Lactobacillus spp. and Pediococcus spp.)	Reduced Salmonella infection in chicken	Higgins et al. (2011)
P. acidilactici-based probiotic	Enhanced the resistance of birds against coccidiosis	Lee et al. (2007)
Probiotic *B. subtilis* (BP6)	Controlled necrotic enteritis due to *C. perfringens*	El Kady et al. (2012)
LAB culture alone or combined with MOS	Reduced the *C. perfringens*-associated mortality	Hofacre et al. (2003)
Synbiotic (*E. faecum* plus FOS)	Prevented necrotic enteritis induced by *C. perfringens* as comparable to salinomycin	El-Ghany (2010)
Formic acid	Decreased *Salmonella* infection in the chicken	Van Immerseel et al. (2006)
Propionic acid	Alleviated turkey poult enteritis and mortality syndrome	Roy et al. (2002)
Enzyme β-mannanase	Reduced the severity of challenge by *Eimeria* sp. and *C. perfringens* (reduced lesion scores in the intestine)	Jackson et al. (2003)
Dietary n-3 PUFAs (combination of tuna oil, sunflower oil and palm oil)	Improved the resistance of chicken against IBD	Maroufyan et al. (2012)
Dried leaf of *Artemisia Annua*	Reduced lesion scores attributable to *E. tenella* infections	Allen et al. (1997)
Artemisinin in *Artemisia sieberi*	Reduced the severity of coccidial infection induced by *E. tenella* and *E. acervulina*	Arab et al. (2006)
Epimedium polysaccharide and propolis flavones	Inhibited the cellular infectivity of ND virus and improved the curative effect of ND in chicken	Fan et al. (2011)
Essential oil of *Oreganum aetheroleum*	Was effective for the treatment of *E. coli* infection in broiler chicken when compared with antibiotic containing ciprofloxacin	El-Ghany and Ismail (2013)
Apacox (extracts from the plants *Agrimonia eupatoria*, *Echinacea angustifolia*, *Ribes nigrum* and *Cinchona succirubra)*	Exerted a coccidiostatic effect against *E. tenella*	Christaki et al. (2004)

5. Nutraceuticals for prevention and/or treatment of enteric infections in poultry

Considering the potential benefits of nutraceuticals in modulating the gut microbial populations and immune systems of the chicken, the use of nutraceuticals for prevention and/or treatment of enteric infections has been the subject of intense studies. Apart from the successful attempts (Table 5), some unsuccessful attempts to control the enteric infections in chicken using nutraceuticals have also been reported. For example, Vidanarachchi et al. (2013) reported neither the plant extracts nor the commercial prebiotic products were effective in controlling necrotic enteritis. Similarly, Hofacre et al. (2003) reported neither addition of FOS or MOS to the chicken diet had a significant effect on mortality caused by necrotic enteritis. The wide variety of the nutraceuticals used in the studies (including type, sources and dose of nutraceuticals) and different types of enteric infections may explain these results discrepancy.

6. Conclusions

The potentials of nutraceuticals in improving the gut ecosystem and immune functions of chicken may reasonably translate the potential of these compounds as the nutritional tools for growth promotion as well as for the prevention and/or treatment of enteric infections in poultry. Further studies with larger datasets are needed to confirm the benefits of nutraceuticals before being used in the commercial poultry industry.

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